History of Bioequivalence for Critical Dose Drugs

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Office of Pharmaceutical Science
April 13, 2010

Definition of Bioequivalence (BE)

The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1

Early History

- 75/75 (or 75/75 – 125) rule was originally proposed in the late 1970s as an alternative means of testing the bioequivalence of two formulations of a pharmaceutical agent.
- Specified that the ratio of test-to-reference formulation of a bioavailability measure arising in a bioequivalence study must be between 75 and 125 per cent of unity in at least 75 per cent of subjects to declare two formulations bioequivalent
- Rule garnered criticism in the literature

History (continued)

- In the early 1980s a “power approach” was applied to AUC and Cmax
- Consisted of two tests – test of null hypothesis of no difference between formulations and evaluation of the power of the test to detect a 20% mean difference in treatment
- Was used in conjunction with the 75/75 rule at times
- Use of these methods discontinued by the agency in 1986

History (continued)

- Due to public concern about BE, a public hearing was conducted by FDA in 1986
- BE Task Force was formed to investigate the scientific issues raised at the hearing
- Task Force report was released in 1989
- Subsequently, FDA issued guidance on statistical procedures for BE studies in July of 1992

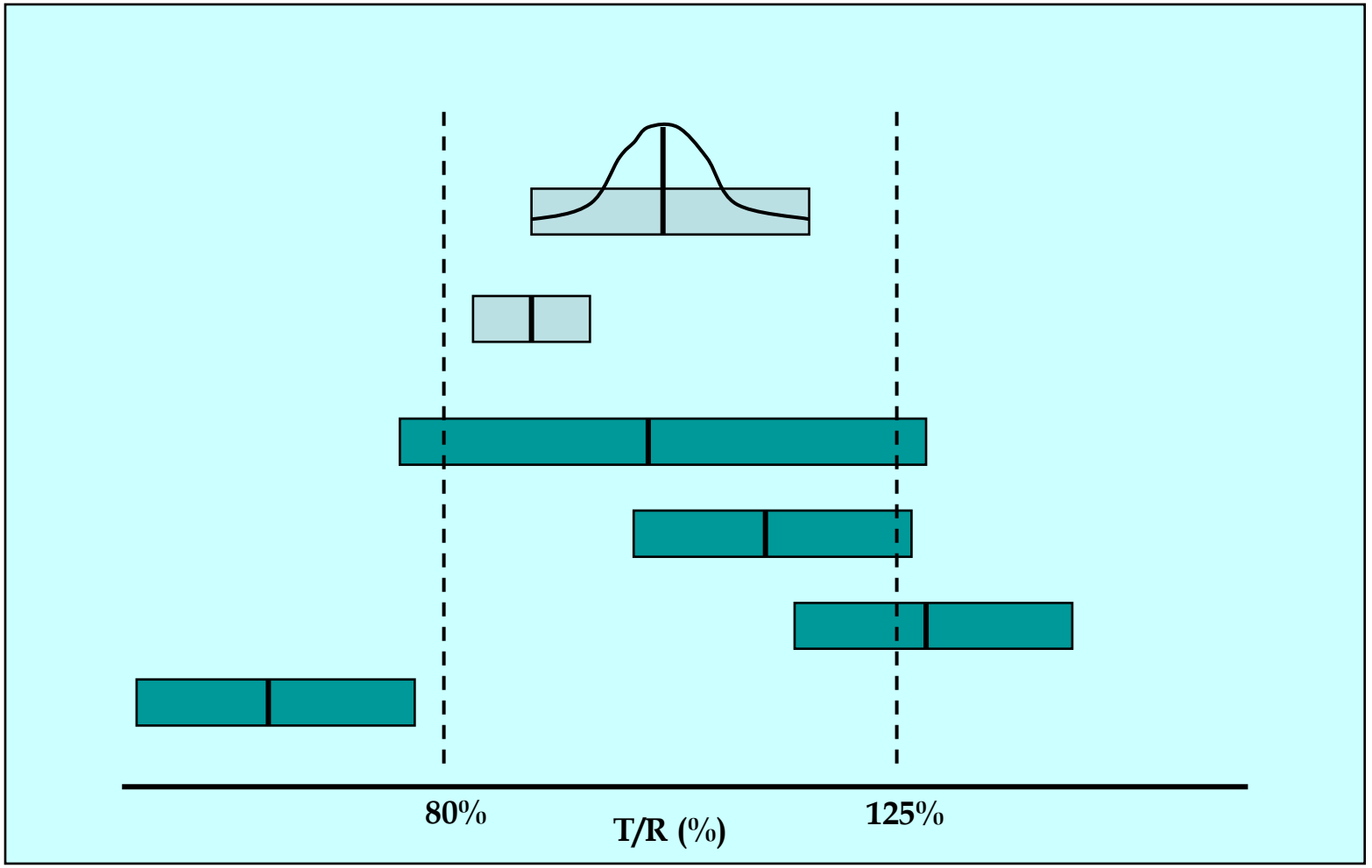
Current Practice

- Two one-sided tests procedure (also called 90% confidence interval approach)
- Recognizes there will be a difference in mean values between treatments
- Provides reasonable assurance that mean treatment differences are acceptable
- Before July, 1992, 90% confidence intervals for AUC and Cmax had to be within the range of 80 to 120% around the RLD mean value
- July, 1992 statistical procedures guidance recommends confidence intervals of 80 – 125% for AUC and Cmax after log transformation

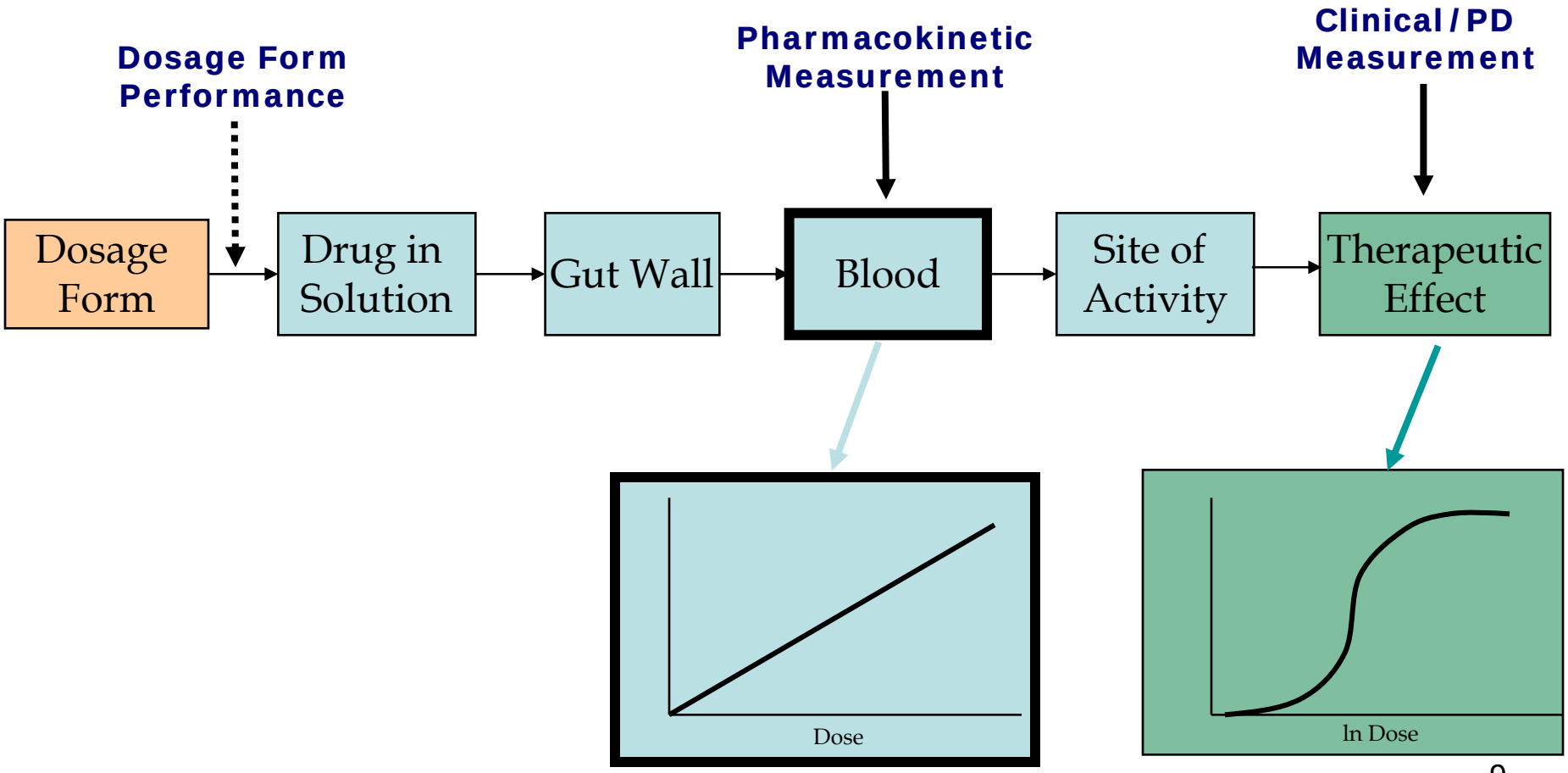
Statistical Analysis

- Bioequivalence criteria
  - Two one-sided tests procedure
    - Test (T) is not significantly less than reference
    - Reference (R) is not significantly less than test
    - Significant difference is 20% (α = 0.05 significance level)
      - T/R = 80/100 = 80%
        - » R/T = 80% (all data expressed as T/R so this becomes 100/80 = 125%)

Possible BE Results (90% CI)



Model of Oral Dosage Form Performance



Critical Dose Drugs

- Drug Products that are subject to therapeutic drug concentration or pharmacodynamic monitoring
  - Examples are: Digoxin, Lithium, Phenytoin, Warfarin
- Traditional bioequivalence limit of 80-125% is unchanged for these products

Considerations for Critical Dose Drugs

- Those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events.
- Up to now have not determined that different BE criteria were needed
- Not necessary for practitioners to view any therapeutic class of drugs differently from any other when FDA had made a determination of therapeutic equivalence
- Nor are additional clinical tests needed when a generic drug is substituted for a brand name
- FDA criticized for this approach

Comparison of Acceptance Criteria Across International Agencies

- BE guidelines were surveyed from Australia, Canada, EU, Japan and South Africa
- All had stricter acceptance criteria for NTI/CD drugs
- Health Canada and the Japanese Nation Institute of Health Sciences publish lists of NTI/CD drugs
- South African Medicine Controls Council publishes a list of “bioproblem” drugs that includes NTI/CD drugs
- European Agency for the Evaluation of Medicinal Products (EMEA) and Australian Therapeutic Goods Administration to date have not published list of NTI/CD drugs

Canada – Health Canada

- Usual BE Acceptance Criteria
  - AUC – 90% Confidence Interval (CI) of T/R ratio should fall within 80 – 125%
  - Cmax – T/R point estimate should fall within 80 – 125%
- Recommended BE Acceptance Criteria for Generic CD Drugs
  - Both AUC and Cmax – 90% CI of T/R ratios should meet acceptance criteria
  - AUC – 90 – 112%
  - Cmax – 80 – 125%
- Drugs considered NTI

Cyclosporine	Digoxin	Flecainide	Lithium
Phenytoin	Sirolimus	Theophylline	Warfarin

European Union – EMEA

- Usual BE Acceptance Criteria

  Both AUC and Cmax – 90% CI of T/R ratios should fall within 80 – 125%
- Recommended BE Acceptance Criteria for Generic NTI Drugs
- Both AUC and Cmax – the usual 80 – 125% acceptance interval “may need to be tightened”
- Has No Listing of NTI Drugs

Japan – NIHS

- Usual BE Acceptance Criteria

  Both AUC and Cmax – 90% CI of T/R ratios should fall within 80 – 125%

- Recommended BE Acceptance Criteria for Generic NTI Drugs

  No change in acceptance criteria for AUC and Cmax; however, if dissolution profiles of lower strengths of modified-release NTI drugs are not “equivalent” (f2 analysis) to corresponding reference product profiles, then in vivo studies must be done (no biowaivers)

- List of 26 NTI Drugs – includes Digoxin, Lithium, Phenytoin, Tacrolimus, Theophylline, Warfarin; adds others such as Carbamazepine, Ethinyl Estradiol, Quinidine

South Africa – MCC

- Usual BE Acceptance Criteria
  AUC – 90% CI of T/R ratio should fall within 80 – 125%
  Cmax – 90% CI of T/R ratio should fall within 70 – 133%
- Recommended BE Acceptance Criteria for Generic NTI Drugs
  Both AUC and Cmax – 90% CI of T/R ratios should fall within 80 – 125%
- List of "Bioproblem" Drugs (37) that includes NTI Drugs; Substitution guideline states "unless adequate provision is made for monitoring the patient during the transition period, substitution should not occur when prescribing and dispensing generic mediations that:
  - Have a narrow therapeutic range;
  - Have been known to show erratic intra-and interpatient responses;
  - Are contained in dosage forms likely to give rise to clinically significant bioavailability problems (i.e., superbioavailability); or
  - Are intend for the critically ill and/or geriatric or pediatric patient"

Australia – TGA

- Follows EMEA guidelines for usual BE acceptance criteria and recommended BE criteria for generic NTI drugs
- Has no list of NTI drugs

NOTE

All five regulatory agencies discussed, request log-transformation of AUC and Cmax data for BE statistical analysis

Committee Input

- FDA has been criticized for having a “one size fits all” BE criteria
- FDA determined it was time to re-evaluate the current position
- Need the Committee’s advice on whether to change the BE acceptance criteria for critical dose products and, if so, what criteria would be appropriate

Interchangeability of Critical-Dose Drugs: Clinical Perspectives

Laurie Frueh, MD

Medical Officer

Office of Pharmaceutical Sciences

What is a Critical Dose Drug?

- Narrow therapeutic ratio:
  - less than a 2-fold difference in median lethal dose (LD50) and median effective dose values (ED50), -or- less than 2-fold difference in the minimum toxic concentrations (MTC) and minimum effective concentrations (MEC) in the blood
- Critical dose drugs:
  - those drugs in which comparatively small differences in dose or concentration may lead to serious therapeutic failures and/or serious adverse drug reactions

- variety of terms:
  - narrow therapeutic index
  - narrow therapeutic range
  - narrow therapeutic ratio

-narrow therapeutic window

- critical dose drugs

U.S. Food and Drug Administration. Title 21 Code of Federal Regulations (CFR) 320.33, Office of the Federal Register, National Archives and Records Administration, 2006. 38. Health Canada. *Guidance for Industry, "Bioequivalence requirements: Critical Dose Drugs",* May 31, 2006.

Which Drugs are Considered to be Critical Dose?

- Agency does not formally designate specific critical dose/NTI drugs
- Major drug classes
  - Antiepileptics
  - Antiarrhythmics
  - Immunosupressives
  - Anticoagulants
  - Others…
- Possible examples
  - phenytoin, digoxin, cyclosporine, warfarin, levothyroxine, theophylline

Why the controversy?

- ongoing differences of opinion among healthcare providers, scientists, regulatory agencies, pharmaceutical companies, and consumer advocates
  - whether the current BE criteria are appropriate for all drugs
  - specifically whether critical dose (CD) drugs require special consideration
- some have expressed concern that bioequivalent generic and brand-name CD drugs may not be equivalent in their effects on various clinical parameters

What is the evidence?

Pharmacokinetic Data: retrospective analyses

- FDA quantified differences between generic and innovator products
- 2070 single-dose BE studies evaluated
- Average percent differences between generic and innovator geometric means
  - Cmax average difference: 4.35%
  - AUC average difference: 3.56%
- 98% of BE studies AUC differed by < 10%
- Similar to results from previous FDA studies

Davit BM, et. al. *Ann Pharmacother* 2009;43:1583-1597.
Henney J.E. *JAMA* 1999;282:1995.

Pharmacokinetic Data: prospective & patient populations

- Carbamazepine
  - Nonblinded crossover study: BE and clinical effects of 2 preparations
  - 14 patients, 13 completed study
  - Formulations BE under current standards, slightly higher BA for generic

  (AUC 111.5% [90% CI 105.6-117.8%]; C-max 110.1% [90% CI 100.4-117.0%])
  - AEs common, 8 of 13 patients who completed study c/o dizziness, nausea, ataxia, etc

- Lamotrigine
  - 9 pts on lamotrigine and who reported problems with formulation switch
  - 5 with PK deviations greater than 90-111%
    - included AUC, Cmax and Cmin
  - 3 patients had deviations in several parameters consistent with original complaint
    - Cmax +21% and complaint of ataxia, Cmax/AUC -15% and breakthrough seizure

Mayer T, et al. *Clinical Drug Investigation* 1999;18(1):17-26. Nielsen KA, et al. *Epilepsy Behav* 2008;13:1494-1496.

What is the clinical evidence?

- Experimental Studies
  - Randomized controlled clinical trials
- Observational Studies
  - Cohort Studies
  - Case-Control Studies
  - Case Reports, Case Series

Randomized Controlled Clinical Trials

- Challenging to use clinical response to detect therapeutic differences between two products
  - Large population required
  - Cost prohibitive and time consuming

Using a clinical endpoint with a 10% mortality (MI) to show a 20% improvement between drug product (100% BA) and placebo (0% BA) would require 8600 participants.

To compare formulations with 20% difference in BA would require…

Barr WH et al. *Transplantation Proceedings* 1999;31:1645-1648. Yusif, et al. *JAMA* 1998:260:2259.

Randomized Controlled Clinical Trials: Warfarin

- Few small, prospective randomized controlled trials including clinical endpoints comparing generic and innovator warfarin
- Generic and brand performed similarly

SOURCE	# PTS	STUDY DESIGN	OUTCOME
Lee et al, 2005	35	Double blind with crossover	No significant difference in pooled INR or AE frequency. Dose adjustments rare

Lee HL, et al. *Clin Ther* 2005;27(3):309-319.

Cohort Study: Warfarin Substitution

- 210 patients from 2 anticoagulation clinics
- 105 switched to generic formulation for 8 weeks, 105 remained on innovator product
  - Nonrandomized trial but similar characteristics (age, sex, target INR, indication for warfarin)
- Use of generic warfarin in patients previously receiving the innovator did NOT change the INR more than continued use of innovator

	Mean ± S.D. INR					
	All Patients		No Dosage Change		Dosage Change	
Time Period	Conversion Group (n = 105)	Control Group (n = 105)	Conversion Group (n = 74)	Control Group (n = 42)	Conversion Group (n = 31)	Control Group (n = 63)
Before enrollment	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.3	2.7 ± 0.4	2.6 ± 0.4	2.6 ± 0.5
After enrollment	2.7 ± 0.5	2.8 ± 0.5	2.6 ± 0.4	2.7 ± 0.4	2.9 ± 0.7	2.9 ± 0.7

Swenson C, et al. *Am J Health-Syst Pharm.* 2000; 57:452-5.

Warfarin retrospective analysis

- 975 patient records identified
- Compared 6 month period before switch with 6 month period after switch
- Estimated warfarin doses increased by 26.5%
- INR decreased by 4.2%
- Limitations to study
  - Retrospective
  - Chart review
  - Did not account for other factors affecting dose-response

	Period 1	Period 2
Warfarin Dose		
• age < 65 (n=290)	• 3.9	• 5.0
• age >65 (n=685)	• 3.3	• 4.2
• overall median	• 3.4	• 4.3
• range	• 0.5 – 10.0	• 0.7 – 15.0
INR		
• median	• 2.4	• 2.3
• range	• 1.2 – 5.6	• 0.9 – 4.8

Halkin H et al. *Clin Pharmacol Ther* 2003;74:215-21.

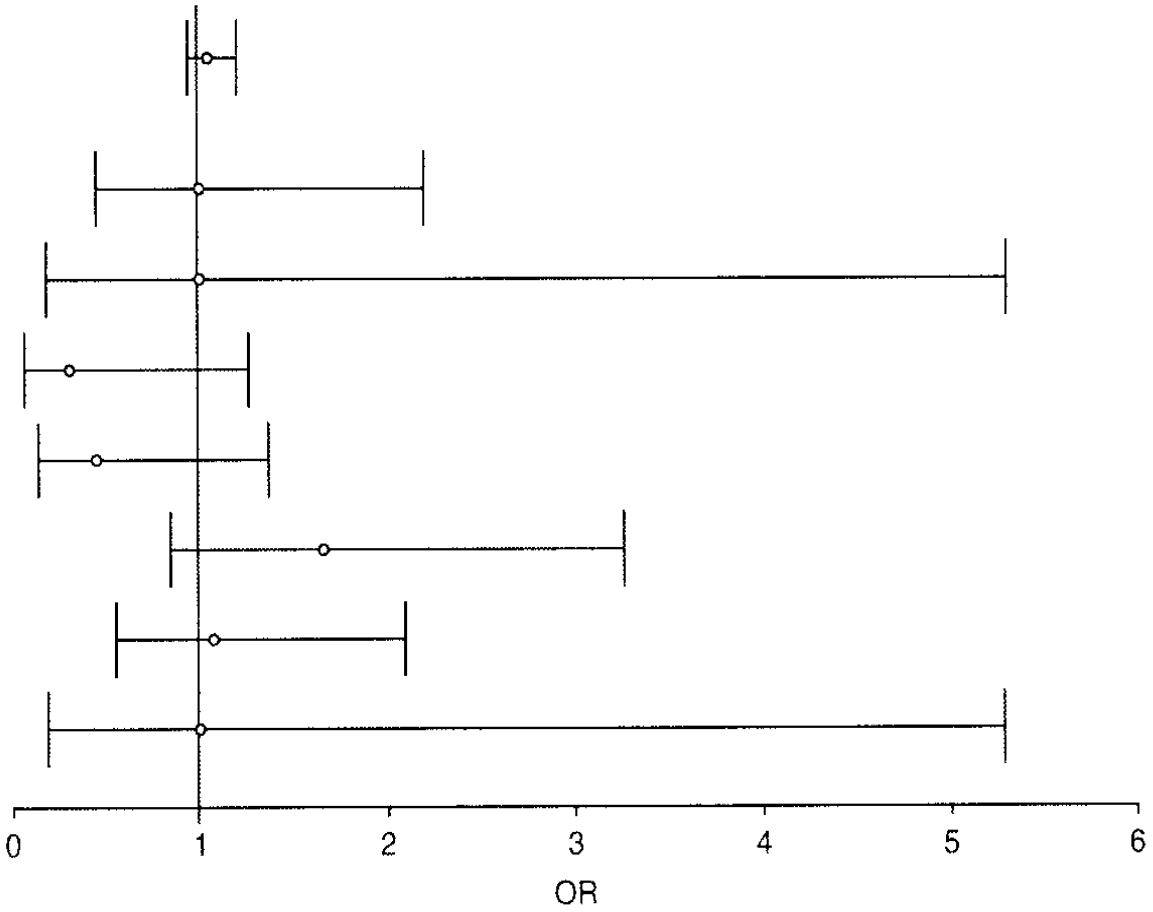
Meta-analyses and Systematic Review: AEDs

- Randomized Clinical Trials
  - 7 included in meta-analysis
  - n = 204
  - OR = 1.1 (95% CI 0.9, 1.2)
  - No difference in the odds of uncontrolled seizure for pts on generic compared with brand
- Observational studies
  - Identified trends in drug or health services utilization that the authors attributed to changes in seizure control

Kesselheim A et al. *Drugs* 2010;70(5):605-621.

Meta-analyses: AEDs

Study name	n	OR	95% CI
All studies	204	1.1	0.9, 1.2
Hartley et al.	22	1.0	0.5, 2.2
Jumao-as et al.	10	1.0	0.2, 5.3
Kishore et al.	60	0.3	0.1, 1.3
Oles et al.	20	0.4	0.1, 1.4
Silpakit et al.	18	1.7	0.8, 3.3
Vadney and Kraushaar	64	1.1	0.5, 2.1
Wolf et al.	10	1.0	0.2, 5.3



Kesselheim A et al. *Drugs* 2010;70(5):605-621.

Case-Control Analyses: AEDs

- Case control Study 1:
  - 416 cases matched 1:3 with 1248 controls of similar age and with same seizure diagnosis
  - 81% greater chance of AED switch for cases (11.3%) than for controls (6.5%)
- Case control Study 2:
  - 991 patients who experienced event requiring care compared with 2973 controls
  - Pts requiring acute care were 80% more likely than matched controls to have had AED substitution

Zachry WM 3rd, et al. *Epilepsia* 2009;50(3):493–500. Rascati KL, et al. *Pharmacotherapy* 2009;29(7):769–774.

Case Series/Case Reports

- Muliple case reports of patients having problems after a formulation switch for a variety of CD drug products
  - Descriptive, but anecdotal, cannot draw conclusions
- Case series
  - 11 patients on phenytoin identified with increased seizure frequency over 5-month period (8 included in study)
  - Mean total phenytoin serum concentrations:
    - on brand was 17.7 +/- 5.3 mg/L
    - on generic 12.5 +/- 2.7 mg/L
    - on reintroduction of brand 17.8 +/- 3.9 mg/L
  - Retrospective, small sample size, no control

Burkhardt RT, et al. *Neurology* 2004;63(8):1494-1496. Hope KA, et al. *Ann Pharmacother* 2001 Feb;35(2):183-7. Wagner JL, et al. *Pharmacotherapy* 2000 Feb;20(2):240-3. Berg MJ, et al. *Neurology* 2008;71(7):525-530.

What about adverse event reporting?

- Low overall reporting rate
  - .3 – 33%
  - Percentage for any specific drug is unknown
- Well documented biases complicate comparative analyses
  - Weber Effect
  - Secular trending
- Health care provider limitations
  - Often unaware of formulation changes
  - May not attribute clinical changes to product switching

Sachs M et al. *Am Jour Med* 1986; 81;49-55. Moore T et al. *Arch Intern Med* 2007;167(16):1752-1759.

What is the Public Perception of CD Drugs?

Patients

Physicians

Pharmacists

Physician Perception

- Limitations of surveys:
  - Retrospective, nonrandomized, self-reported
- Physicians caring for epileptic patients
  - 606 physician surveys conducted (74% neurologists, 26% GPs)
  - 6359 invited to participate -
    - **29.9% response rate for email recruits, 6.2% postal mail**
    - **60.6% of respondents qualified**
  - 88% concerned about formulation switches
  - 65% had seen breakthrough seizures with switch
- Electrophysiologists
  - 130 electrophysiologists surveyed
  - 64 repondents (49% response rate)
    - 33 reported AE's temporally related to formulation substitutions
    - 15 write "dispense as written" on all antiarrhythmic rxs
    - 18 always or usually allow generic substitution

Reiffel JA, et al. *Am J Cardiol* 2000;85(9):1151-3, A10. Berg MJ, et al. *Epilepsy Behav* 2008;13(4):693-699.

Pharmacist Perception

- Community and Hospital Pharmacists
  - overall support of generic medication use
  - concerns related to generic substitution
  - warfarin, phenytoin, digoxin most concerning
- Transplant pharmacists
  - Pharmacists from 107 transplant centers recruited
  - 59 pharmacists participated
  - 92%: BE testing for NTI's should be conducted in patients
  - 95%: generics of certain NTI drugs should not be dispensed

Kirking D.M., et al. *J Am Pharm Assoc.* 2001;4.
Vasquez EM, et al. *Am J Health-Syst Pharm* 1999;56:615-621.

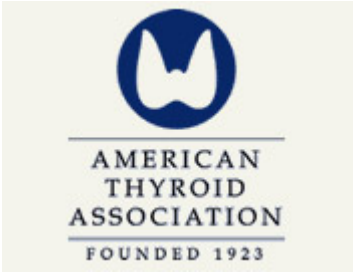
Patient Perception

- Epilepsy Foundation Survey
  - Survey was available on epilepsy foundation website from 2006-2009
  - 1085 respondents
- Patients asked about breakthrough seizures, AED switching, and effects of AED switching on seizure control
  - 79% of respondents had breakthrough seizures
  - 67% of respondents had switched from brand to generic
  - Survey did NOT ask about breakthrough seizures before switch, nor did it further question the 33% who had not switched about their seizure control
- Not a representative sample, self reported data, inherent biases to survey, no control group
- b→g switch: (67%)
  - 59% worsening seizure control
  - 49% worsening side effects
- g→b switch: (40%)
  - 15% worsening seizures
  - 18% worsening side effects

Findings From The Epilepsy Foundation's Survey Of Patient Experiences. November 2006 – March 2009. www.epilepsyfoundation.org. Accessed 22Feb10.

The Epilepsy Foundation, www.epilepsyfoundation.org

Medical Association Positions



American Medical Association

- Generally supportive of generic substitution
- FDA should:
  - More effectively inform physicians of BE standards for generic drugs
  - Additional research evaluating optimum methodology to determing BE
  - Specific Policy Directive: re-examine BE standards for levothyroxine

Generic Substitution of Narrow Therapeutic Index Drugs. Report 2 of the Council on Science and Public Health. American Medical Association. June 2007. Available at http://www.ama-assn.org/ama/no-index/about-ama/17731.shtml.

Other Associations

- AAE, ES, ATA
  - Concerned about current method for determining BE
  - Recommend not to substitute levothyroxine products
- AST
  - Support use of generic NTI immunosuppressives to low-risk transplant recipients with blood monitoring (insufficient data for higher risk)
  - Demonstration of BE in at-risk patients should be incorporated into the generic approval process
- AMCP, ASHP
  - supports allowing pharmacists… to exercise professional judgment when determining whether a generic drug is appropriate

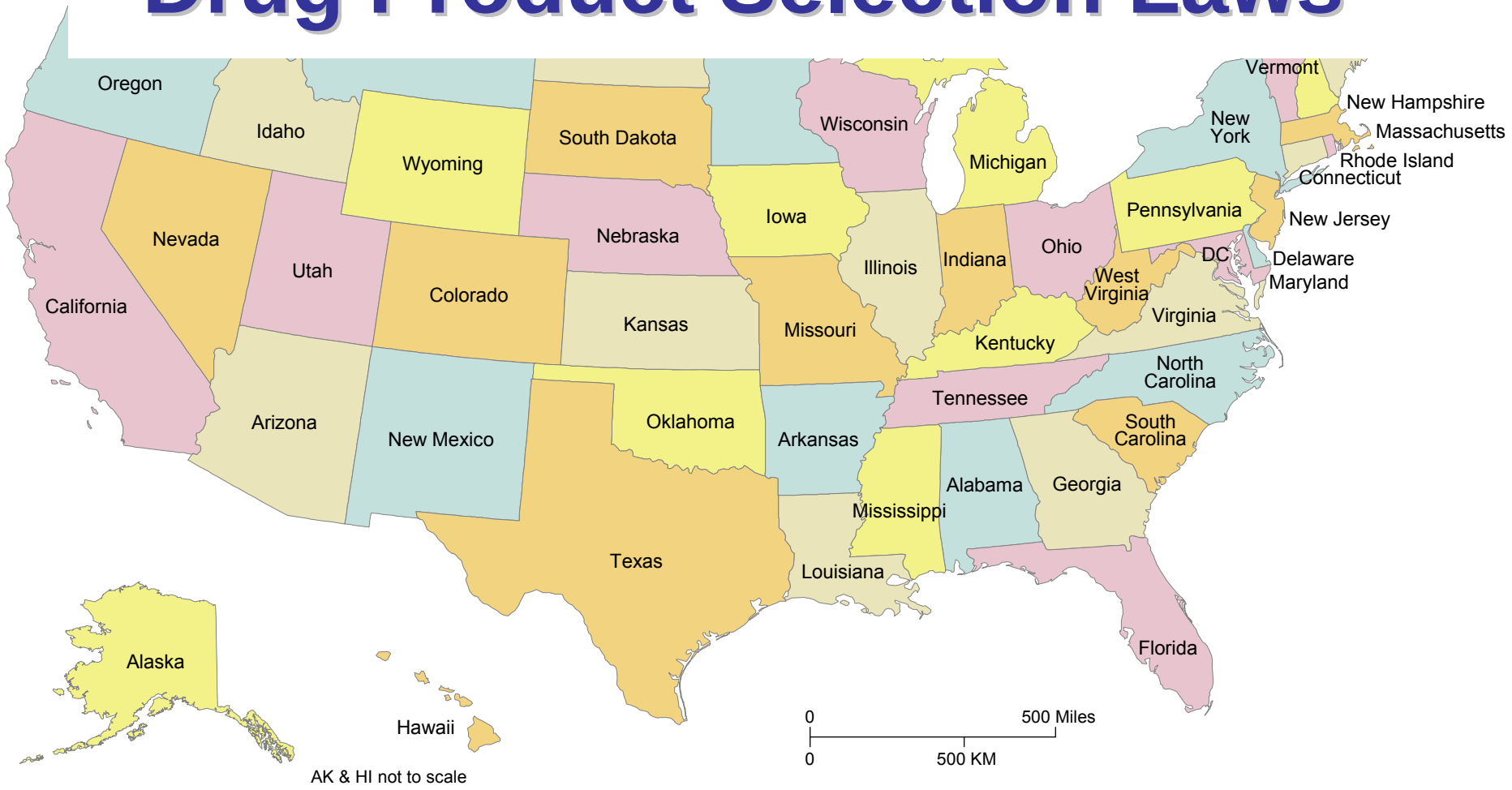
AAE, ES, ATA. Joint Position Statement on the Use and Interchangeability of Thyroxine Products. 2007 AST website. http://www.a-s-t.org . Accessed 07Dec09. Academy of Managed Care Pharmacy. January 28, 2004. www.amcp.org. Accessed February 26, 2010. ASHP Policy Positions. 2003 www.ashp.org. Accessed February 26, 2010.

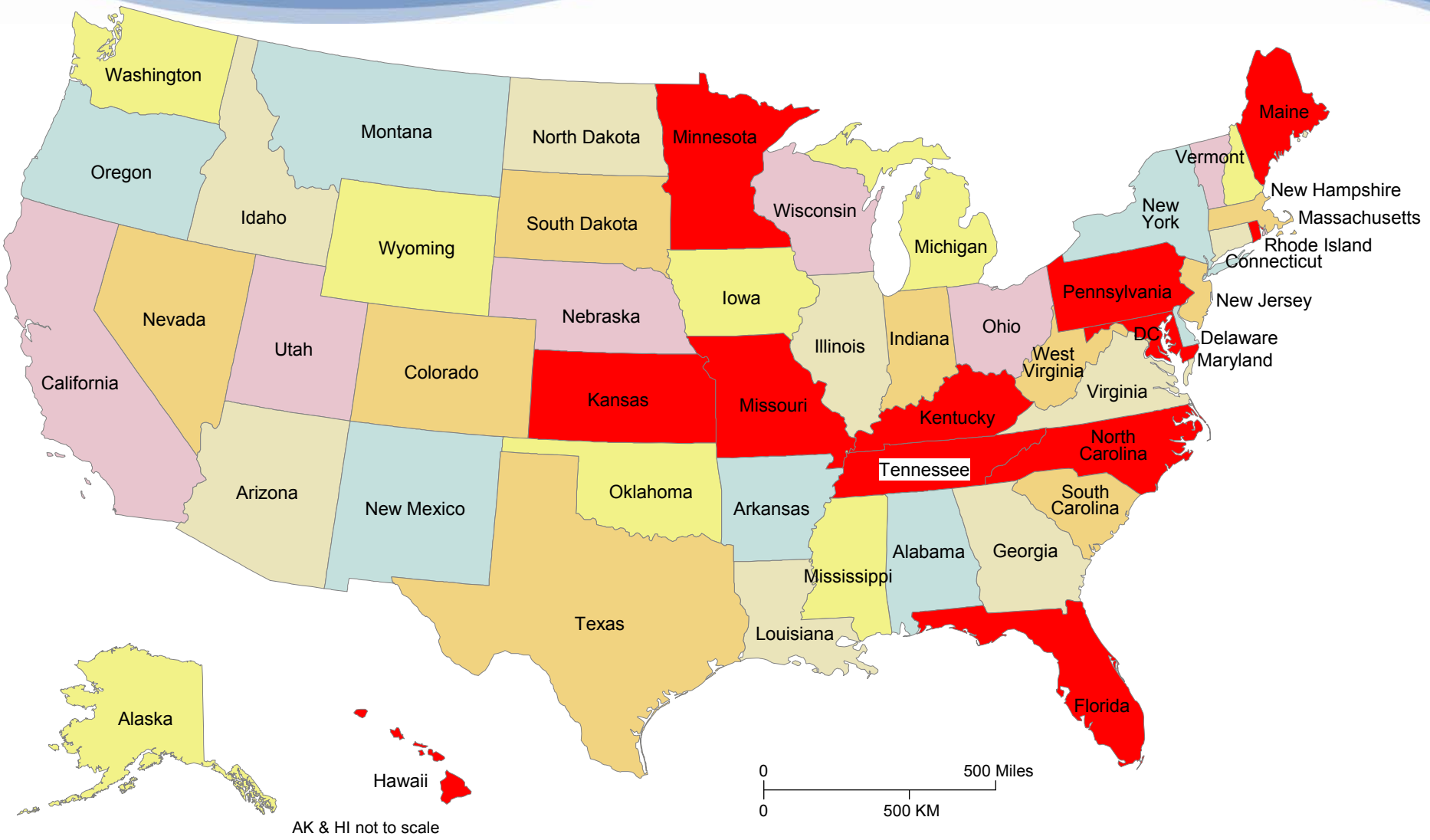
American Academy of Neurology

"The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval"

American Academy of Neurology. Position Statement on the Coverage of Anticonvulsant Drugs for the Treatment of Epilepsy. November 2006.

Drug Product Selection Laws

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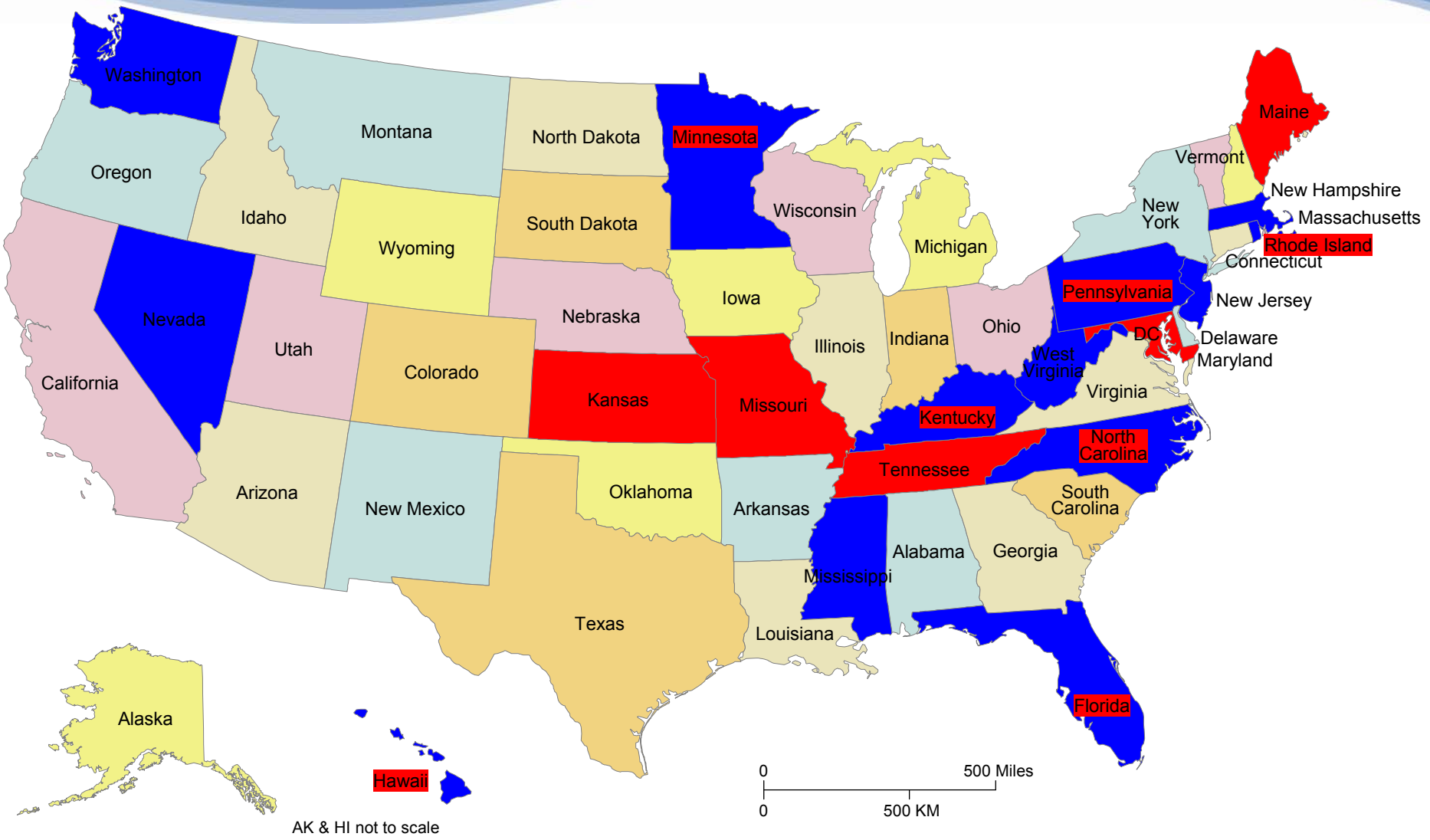
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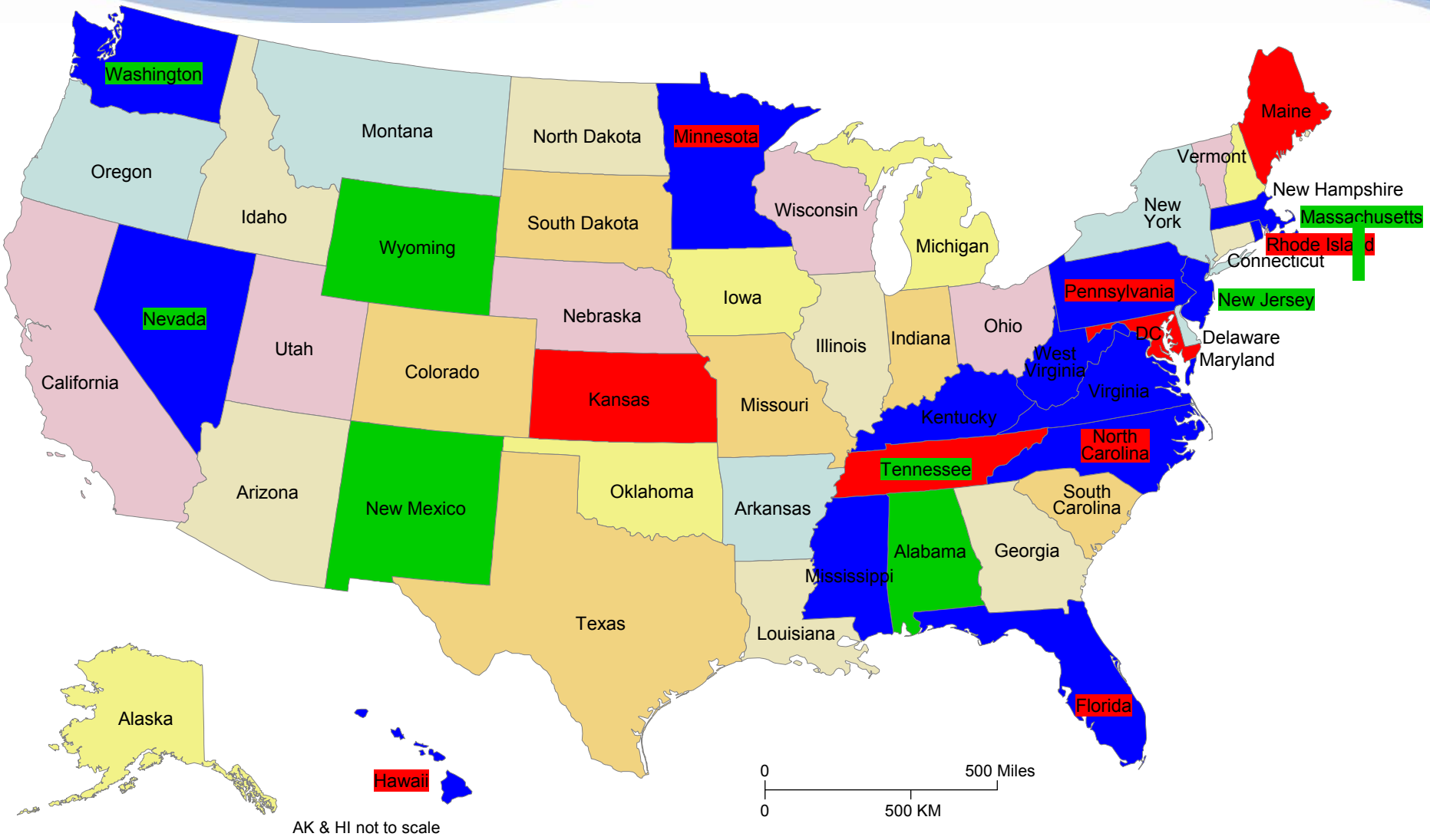
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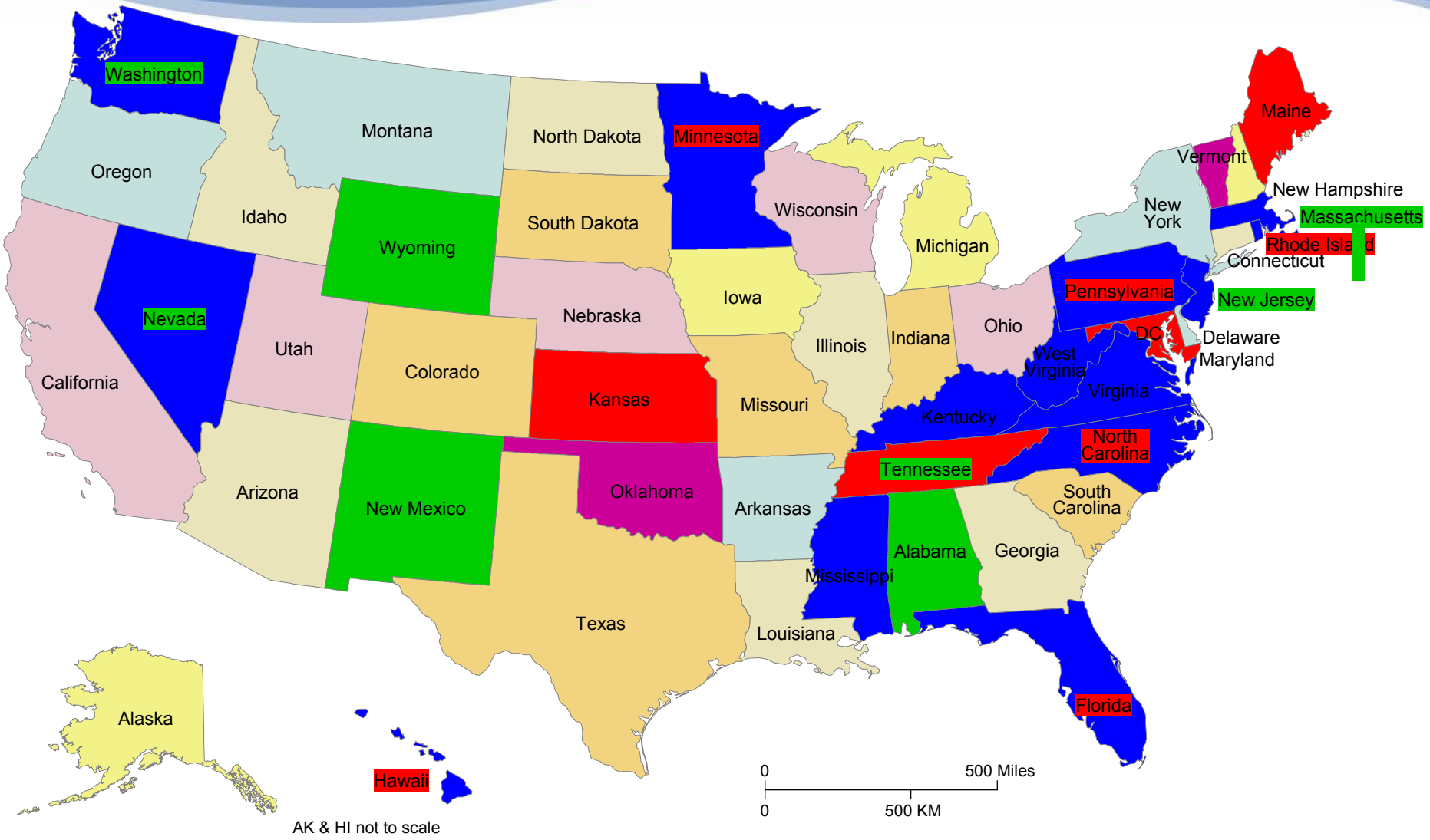
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AK & HI not to scale

Conclusions

- Medical and scientific communities remain divided
  - Conflicting information in the literature as well as mixed messaging from associations and in the media has led to confusion
- Good prospective scientific evidence remains elusive, however:
  - Majority of literature comes from observational studies and case series/report
  - Some question whether the current post marketing system is able to detect clinically significant differences
  - Large scale clinical trials are impractical and unlikely to occur in the near future
- What do we do with the information we have?

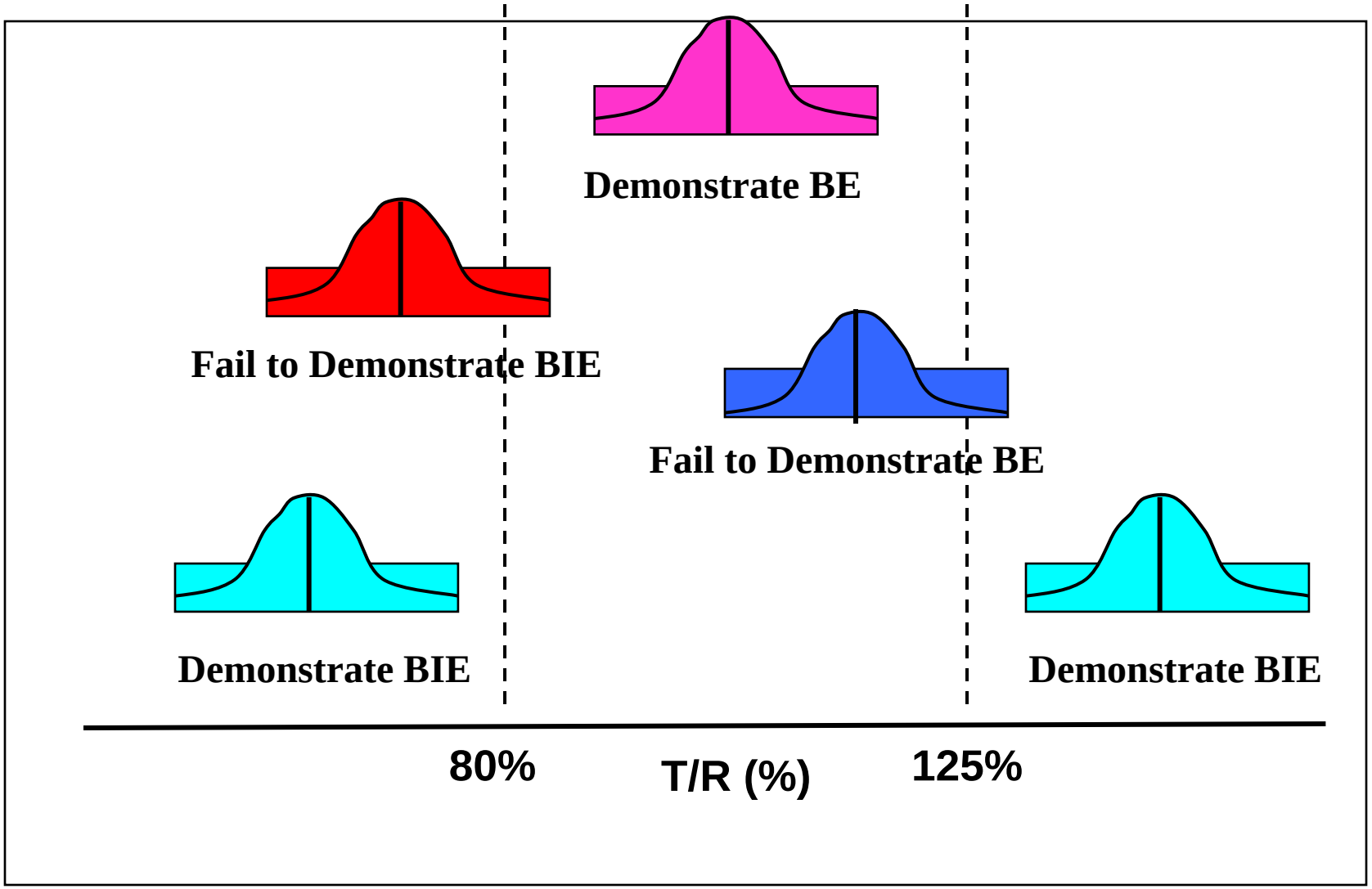
Approaches to Demonstrate Bioequivalence of Critical Dose Drugs

Lawrence X. Yu, PhD.
Deputy Director for Science and Chemistry
Office of Generic Drugs

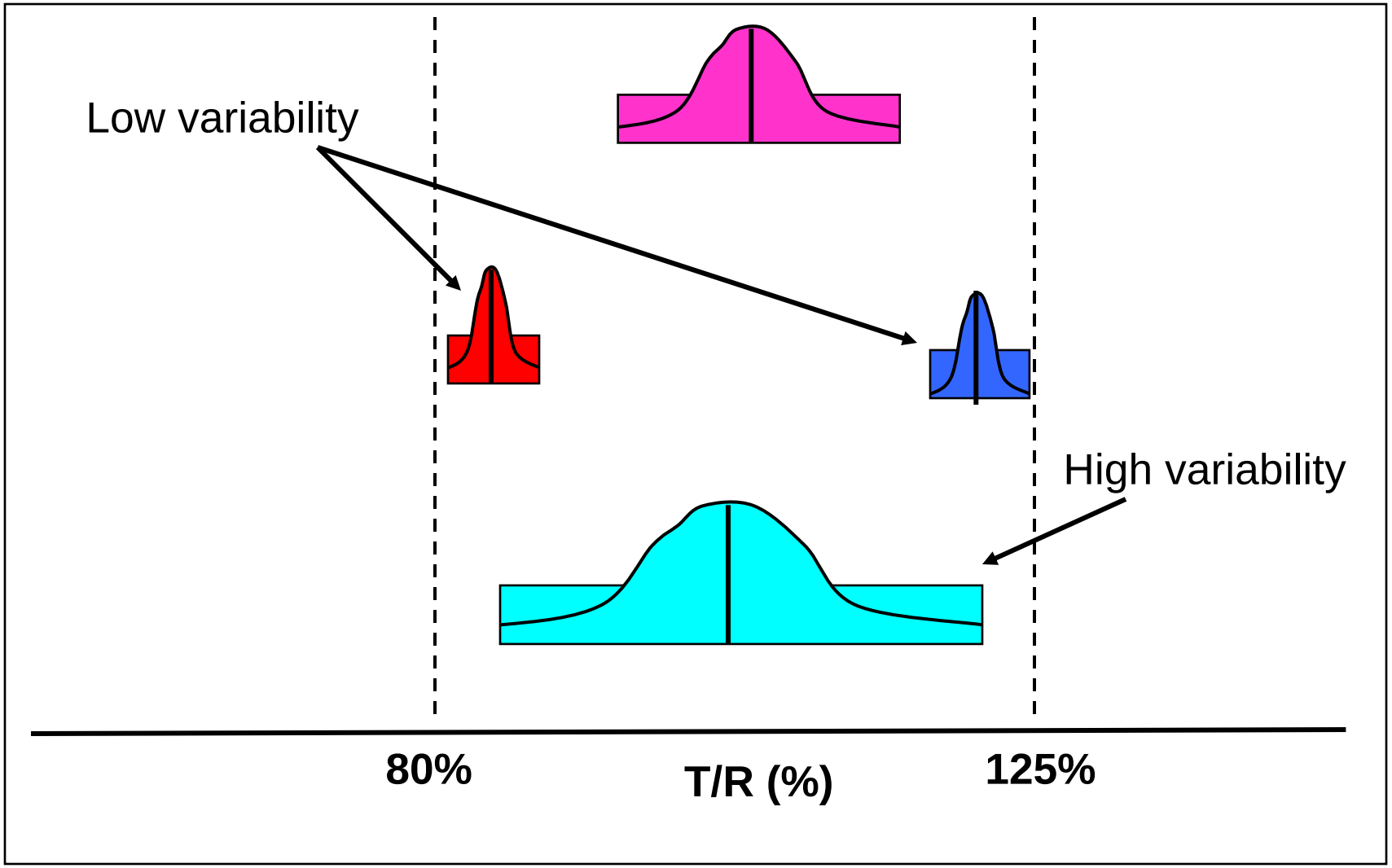
Outline

1. Current BE Approach for Critical Dose Drugs
2. Proposed Alternative Approaches
3. Questions for Committee Members

Possible Outcome of BE Studies



Effect of Variability on BE Studies



CD Drugs Have Low Within-subject Variability

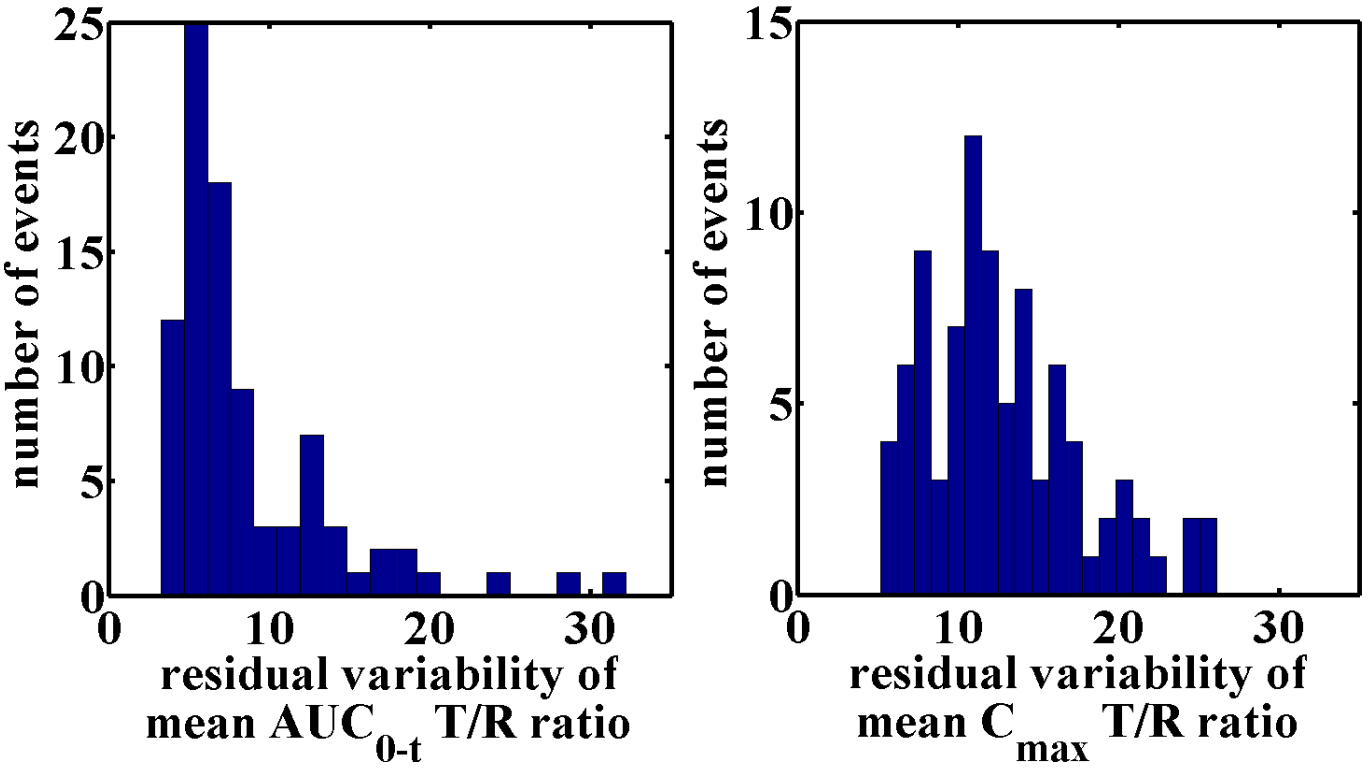
Variability of CD Drugs Frequently Listed in Legislative Bills Proposed in Various States to Limit Generic Substitution of CD Drugs *

Drug	CV% Intersubject	CV% Intrasubject
Carbamazepine	38	
Conjugated estrogens	42	14–15
Digoxin	52	
Levothyroxine sodium	20	<20
Phenytoin sodium	51	10–15
Theophyllin sustained release	31	11–14
Warfarin sodium	53	6–11

* L.Z.Benet. Relevance of Pharmacokinetics in Narrow Therapeutic Index Drugs. *Transplantation Proceedings*, 31, 1642-1644 (1999)

CD Drugs Have Low Within-subject Variability

Distribution of Residual Variability of CD Drugs from 1996-2009 ANDAs (N = 89)



Coefficient of Variation (CV) Varies for CD Drugs

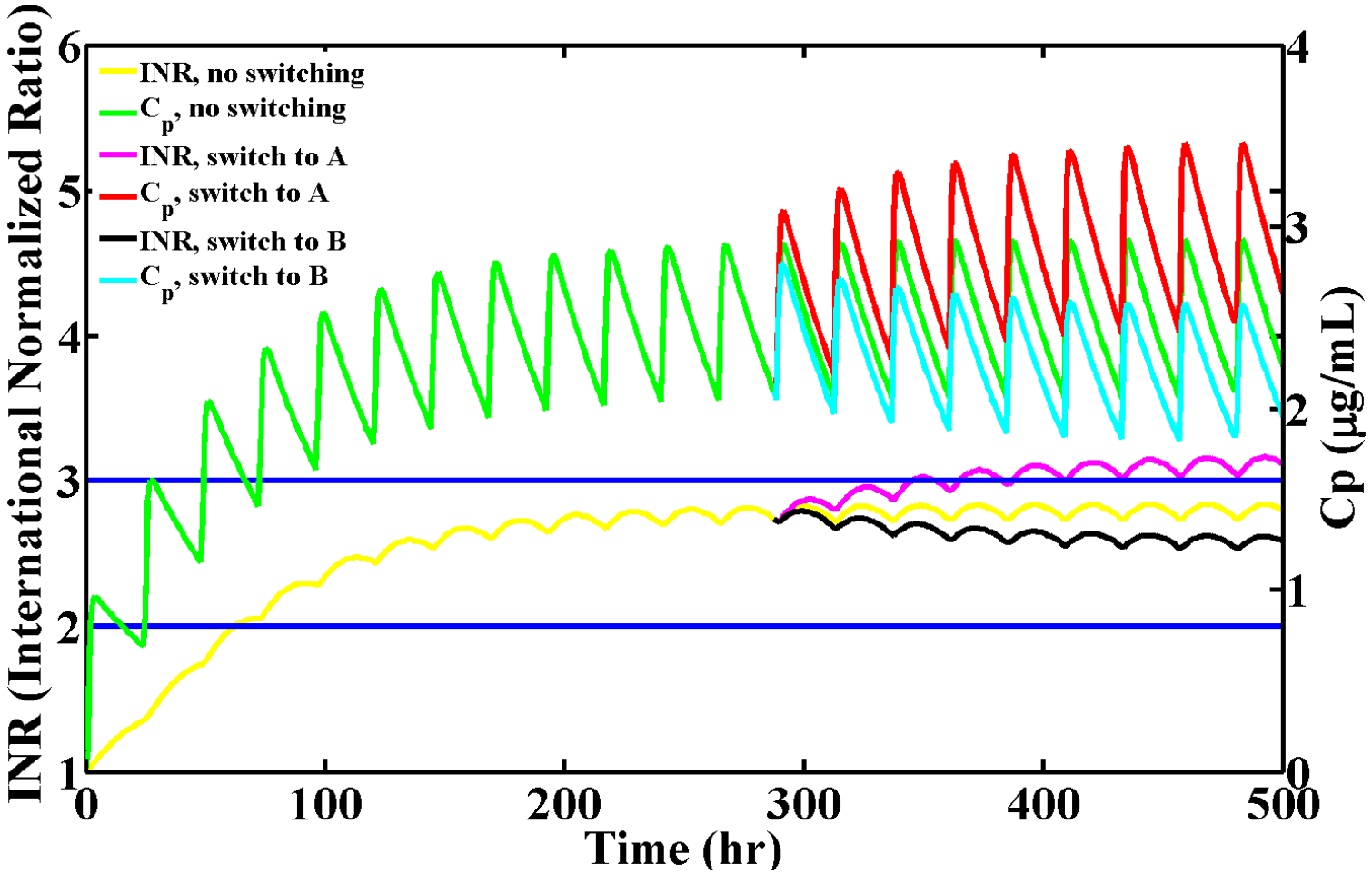
Summary of Residual Variability (% CV) from ANDAs

	AUC_{0-t}		C_{max}	
Drugs	**Mean**	**Range**	**Mean**	**Range**
Warfarin (n=29)	5.7	3.3, 11.0	12.7	7.7, 20.1
Levothyroxine (n=9)	9.3	3.8, 15.5	9.6	5.2, 18.6
Carbmazepine (n=15)	8.0	4.4, 19.4	8.7	5.2, 17.6
Lithium Carbonate (n=16)	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin (n=5)	**21.7**	**13.1, 32.2**	**21.0**	**14.3, 26.1**
Phenytoin (n=12)	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline (n=3)	17.9	12.8, 24.2	18.2	11.8, 25.8

Potential Risks of Applying Current BE Standards to CD Drugs

- Current BE standard: based on assumption that 20% deviation of plasma concentration is not clinically significant.
- For CD drugs: 20% fluctuation in plasma concentration maybe significant.
- CD drugs often have low variability, 90% CI could actually be 85-90% CI or 115-120% CI.
- The CI close to the boundary is highly associated with uncertainty of therapeutic equivalence.
  - Switching between 85-90% and 115-120% CI generic products

Example of 20% or More Changes Could Lead to Toxicity, Theoretical



	P.E.
A/RLD	
AUC_{24}	1.19
C_{max}	1.19
B/RLD	
AUC_{24}	0.88
C_{max}	0.88

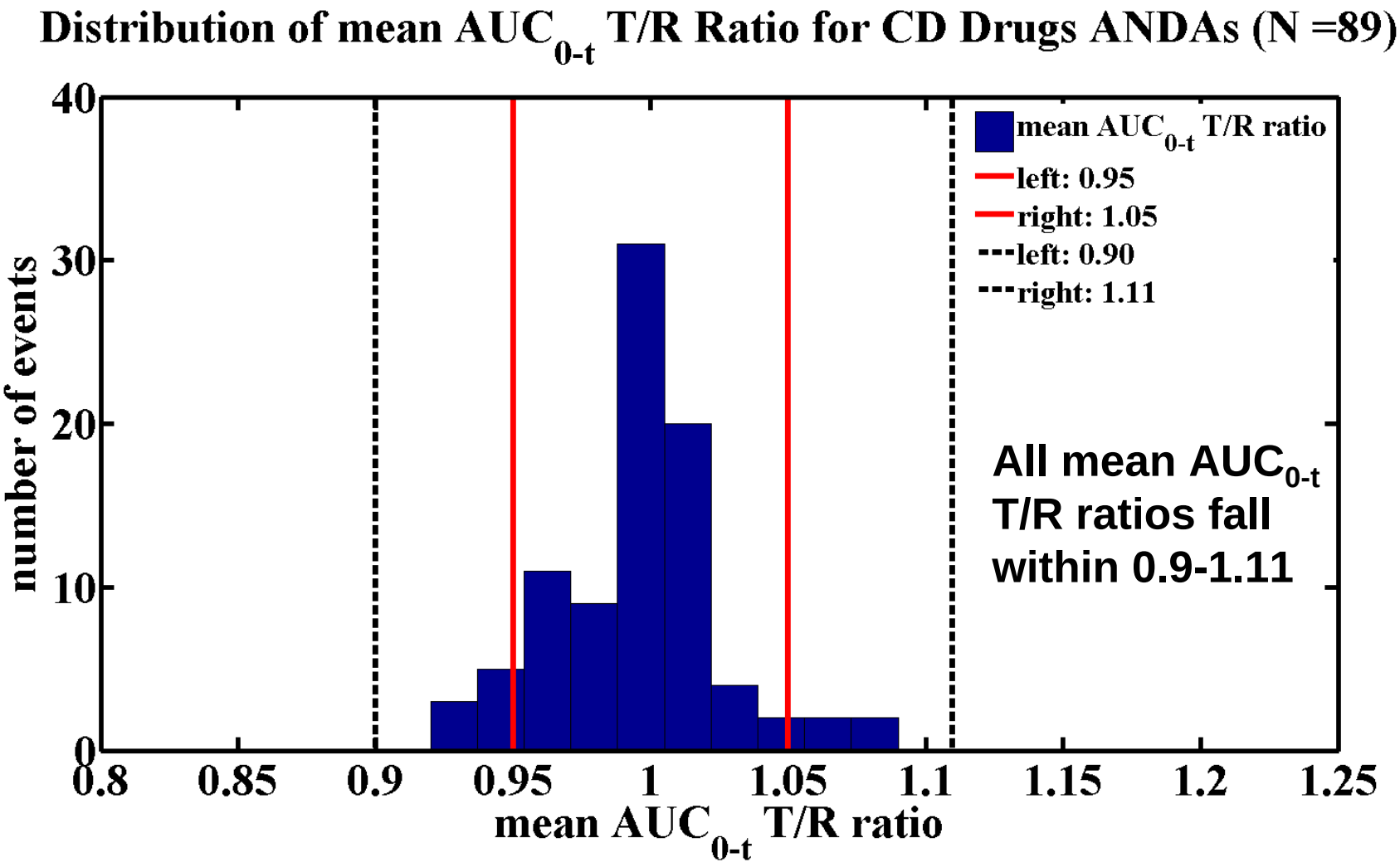
AUC_{24} is the AUC for 24 hours at steady state.

PE: point estimate

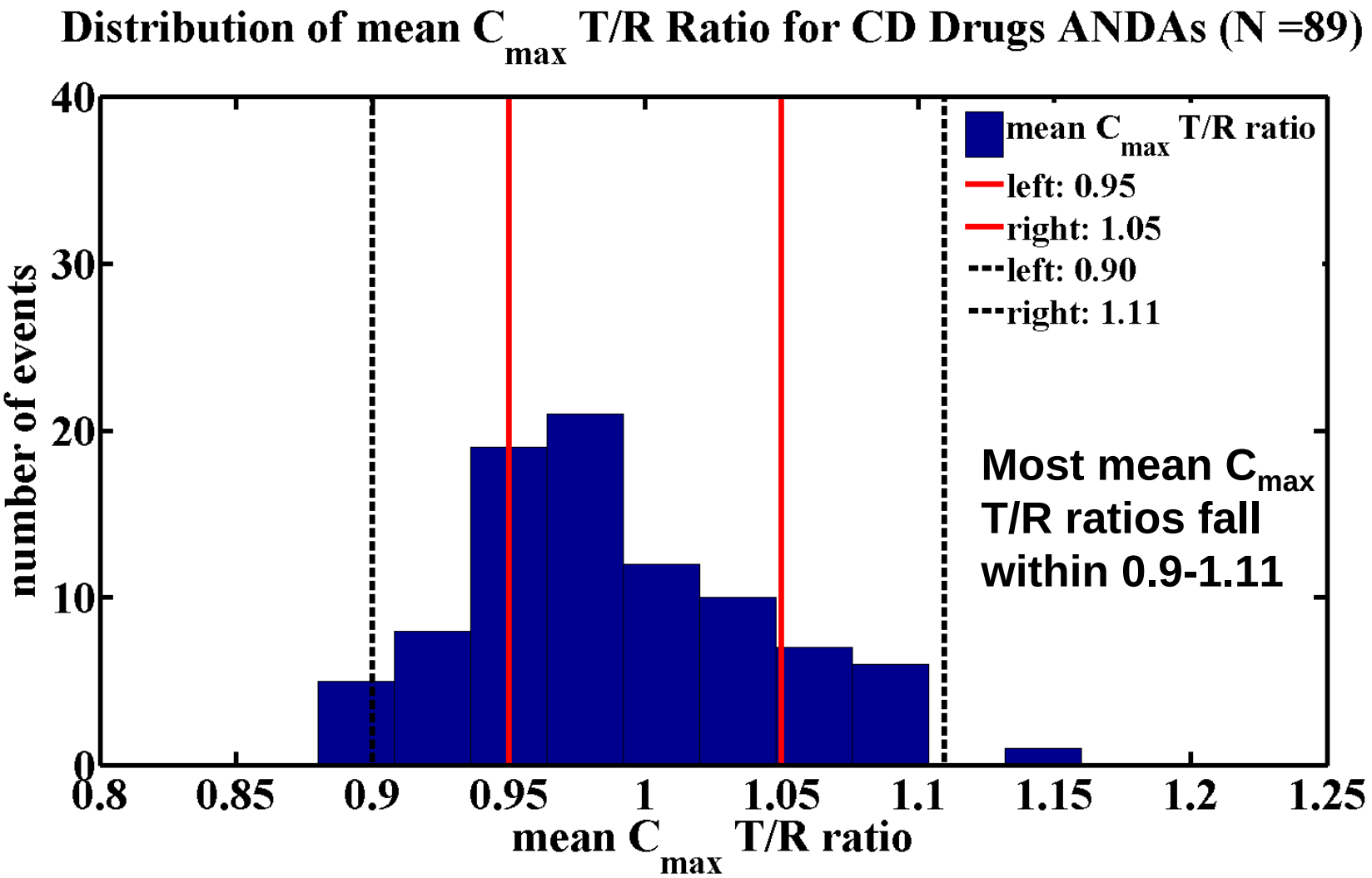
Potential Approaches for FDA

1. Point estimate on AUC within 90-111%
2. Point estimate on AUC within 95-105%
3. 90% CI on AUC within 90-111%
4. 90% CI on AUC within 95-105%
5. 90% CI must include 100%
6. Replicate design study with limits set by variability of the reference product

Impact of Tighter CI



Impact of Tighter CI



Impact of Tighter Criteria on ANDAs

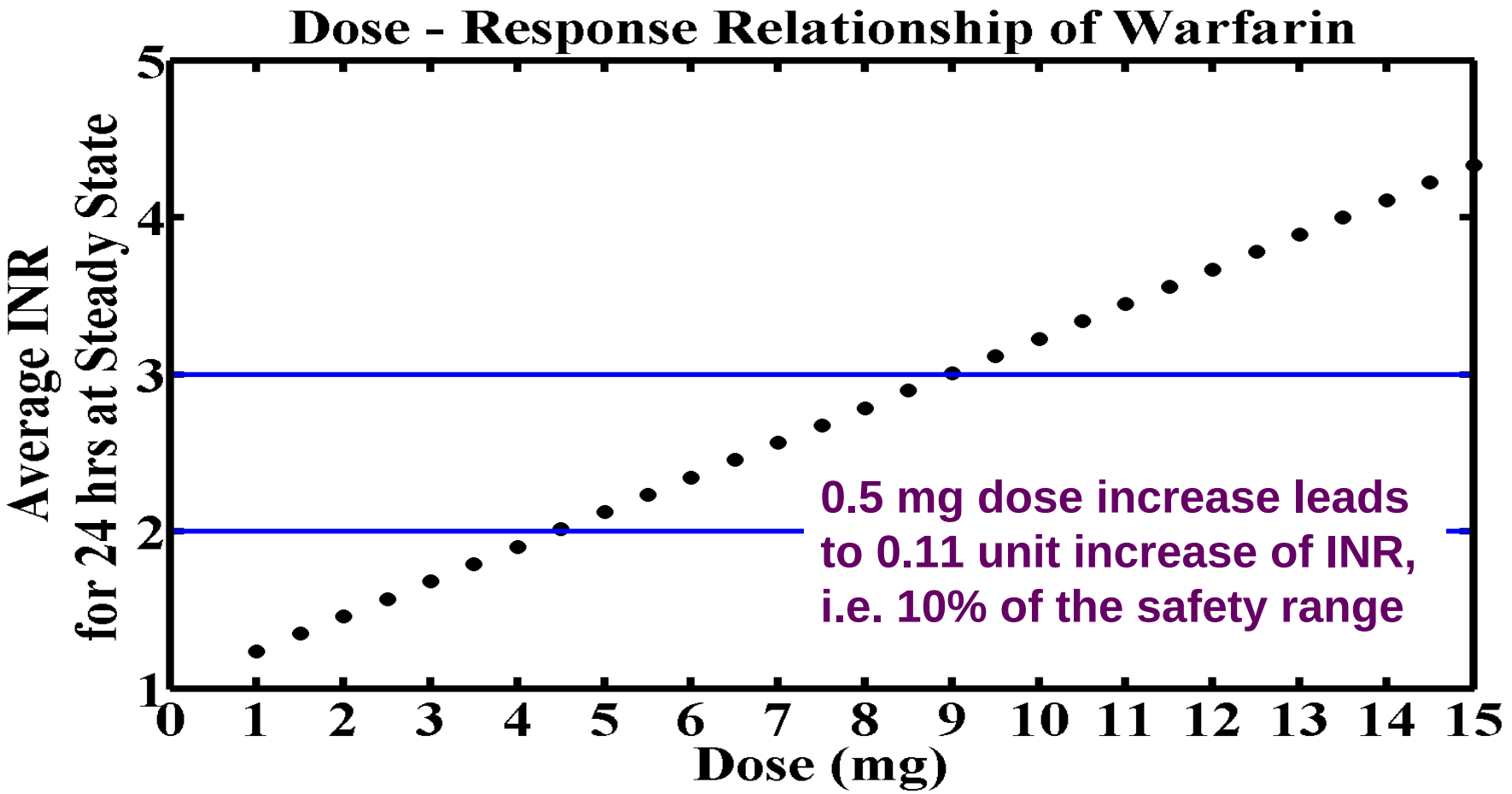
% of ANDAs that will pass tighter criteria

(N = 89)	**AUC_{0-t}**	**C_{max}**
CI includes 1.0	84.3	69.7
CI within [90, 111]	86.5	60.7
CI within [90, 111] and includes 1.0	77.5	50.6
P.E. within [90, 111]	100.0	95.5

Ensuring Equivalence for CD Drugs

- Tighter BE limits (reducing the range) ensures smaller differences in mean bioavailability
- Differences in variability between products are not addressed by tightening the limits.
- Sources of product variability
  - Formulation design
  - Manufacturing quality
    - Variation in dose uniformity

Equivalence for CD Drugs

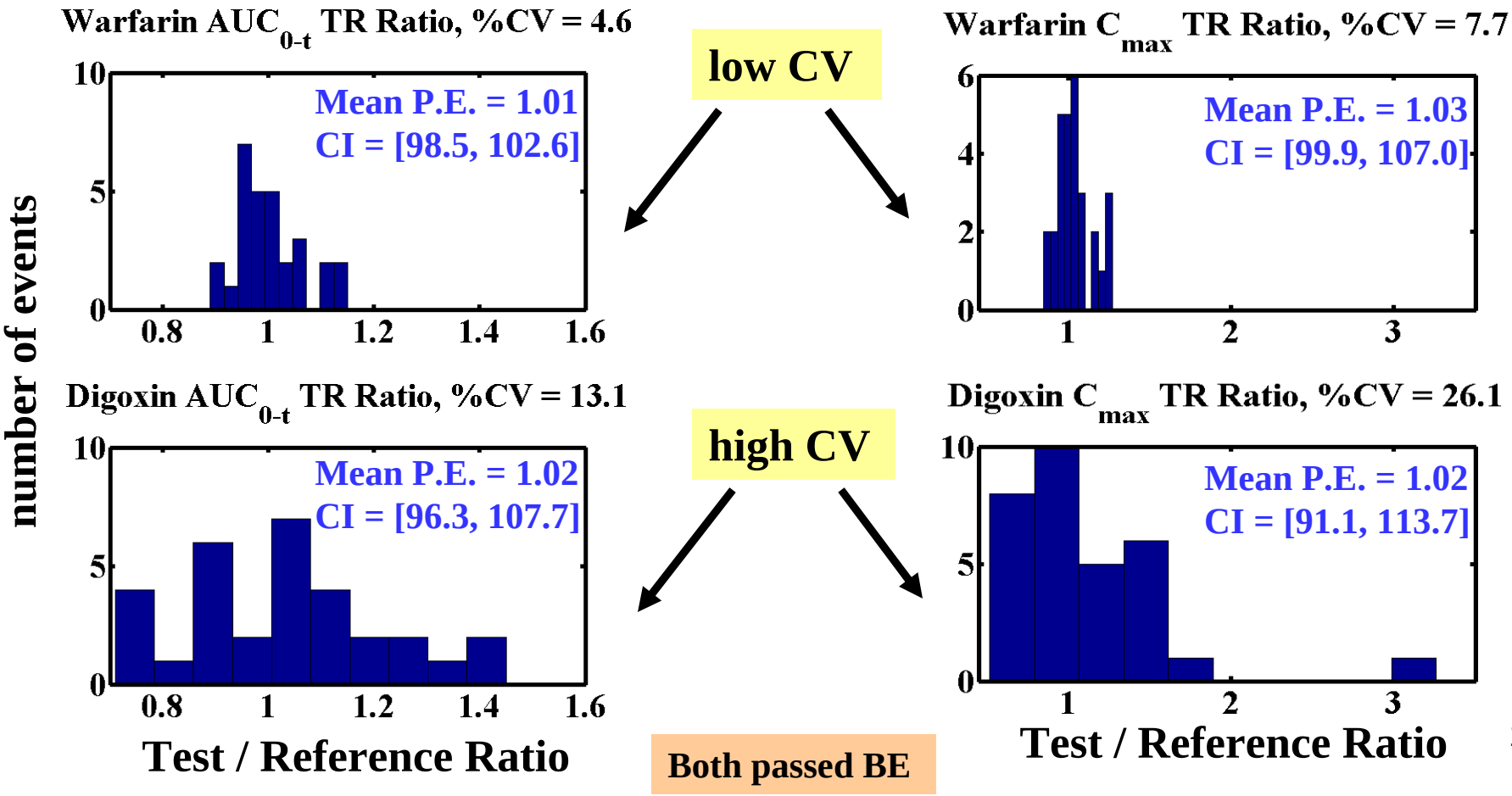


Causes of dose fluctuation are not limited to a change in relative BA upon generic substitution.

Replicate Design Studies

- Provide variability quantification of test and reference products.
  - Comparing T/R distribution to R/R distribution
- Generic substitution should not cause BA variability.
- Reference scaled bioequivalence limits (used for highly variable drugs) naturally tighten the CI.
- Generic product design should not be more variable than the reference product.

Individual T/R Ratios Vary With Passing BE



Reference Scaling

- Mixed scaling method implemented for highly variable drugs
  - Minimum three period (2 R, 1 T) study
  - In mixed scaling, only studies with CV > 30% are scaled
- For CD drugs, should all studies be scaled?
  - As variability of the reference product decreases, the BE limits get smaller

Questions to Committee

1. **Are CD drugs a distinct drug class?**
   a. What terminology should be used to delineate this class and how should it be defined?
   b. Should the FDA develop a list of CD drugs?
2. **Are the current BE standards sufficient for CD drugs?**
   a. Should more rigorous BE standards be adopted?
   b. What should these standards be?
3. **Does the Committee have recommendations for future research?**